REMARKS

Claims 1-4, 6-7, and 9-11 have been examined and are now pending in the application. Reconsideration of all outstanding objections and rejections and reexamination is requested.

SUMMARY OF THE CLAIMED SUBJECT MATTER:

CLAIM 1

The subject matter recited in claim 1 includes the steps cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5), and assigning unique codes to each of the micro dissected section samples that indicate tissue space coordinates of the micro dissected sections samples in the multidimensional morphological matrix of image data (Application at page 8 lines 8-10).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24). This biological data is spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data indicated by the code assigned to the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 4

The subject matter recited in claim 4 includes the steps of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), histologically staining and coverslipping a first set of serial samples for light microscopy (Application at page 7, lines 25 and 26); constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), mounting and covering a second set of serial sample sections with a micro dissection membrane (Application at page 7, lines 27-28), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7 line 33 to page 8, line 5), providing a set of coded micro dissected section sample holders, with each coded micro dissected section sample holder having a code indicating a unique tissue space coordinate in the multidimensional morphological spatial matrix of image data (Application at page 8, lines 6-9), transferring each micro dissected section sample to a coded micro dissected section sample holder

having a code indicating the location of a transferred micro dissected section sample in the multidimensional morphological spatial matrix of image data (Application at page 8, lines 6-9).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24). This biological data is spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data indicated by the code assigned to the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 7

The subject matter recited in claim 7 includes the steps of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7, line 33 to page 8, line 5).

Each coded incised section sample is analyzed to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24). This biological data is linked to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample (Application at page 8, lines 26-34).

CLAIM 11

The subject matter recited in claim 11 includes means for of cutting histologically thin serial sections of a biological sample (Application at page 7, line 22), means for constructing a multidimensional morphological matrix of image data from the serial samples (Application at Fig. 3), means for unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples (Application at page 7, line 33 to page 8, line 5), means for analyzing each coded incised section sample to obtain biological data providing information on a plurality of biological characteristics of the coded micro dissected section sample (Application at page 8, lines 16-24), and means for linking this biological data to the location in the multidimensional morphological matrix of image data indicated by the code of the coded micro dissected section sample (Application at page 8, lines 26-34).

GROUNDS OF REJECTION:

I. Indefiniteness

Claims 1-4, 6, 7, and 9-11 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

II. Obviousness

Claims 1-3, 6, 7, and 9-11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1999, pages 38-41), Farr et al. (P/N 5,811,231), Emmert-Buck et al. (Science, Vol. 274, 1996, pages 998-1001), and Lemelson (P/N 6,058,323).

ARGUMENT:

1. Summary of the Argument

I. The pending claims particularly point out and distinctly claim the subject matter which the applicant regards as his invention and are not indefinite. The phrases pointed out by the examiner are not indefinite when read in light of the disclosure and level of skill in the art.

II. The subject matter recited in the pending claims would not have been obvious to a person of ordinary skill in the art at the time the invention was made.

A. All the limitations recited in claims 1 and 4 are not taught by the cited references as required in MPEP §2143.03.

B. The proposed modification would change the principle of operation of the reference in contradiction of MPEP §2143.01.

C. The cited prior art does not suggest the desirability of the claimed combination as required by MPEP §2143.01

2. Statement of the Arguments

I. Indefiniteness

INDEPENDENT CLAIMS 1, 4, 7, AND 11

The examiner states that the phrase "unattendedly micro dissecting" is vague and indefinite and that it is unclear by what or by whom the micro dissecting is being unattended.

The Office Action states, at page 2, that the claims do not recite "micro-dissection without any selection by an investigator". However, this is clearly the intent of the phrase "unattendedly micro dissecting". As stated at paragraph [35] of the specification:

> A UV laser of the type described in Cole, et al., [Cole, K.A. et al., Nat Genet, 21(1 Suppl):38-41 (1999)] is used to incise a grid pattern across each tissue section of the uncovered set of alternating serial sections described in #1 above. This is done with the use of said UV laser adapted to the application end of a microarray-creation robotic apparatus, as described in Cheung [Cheung, V.G., et al., Nat Genet, 21(1 Suppl):15-9 (1999)]. This allows for unattended section incising of a large number of specimens. A second adaptation of the robotic apparatus [Cheung, V.G., et al., Nat Genet, 21(1 Suppl):15-9 (1999)] adds a microdissection-transfer film holder to the application end of the apparatus. (emphasis added)

Accordingly, a concrete example of unattendedly micro dissecting is the use of the robotic apparatus disclosed by Cheung. Other types of unattended micro dissection may also be described by the phrase. The use of the adverb "unattendedly" to modify the gerund "micro dissecting" is grammatically correct and the meaning is clear when taking into account the detailed description and examples provided in the specification. The lack of a reference to what or who is not attending the micro dissecting does not make the claim indefinite. It is clear from the language that the micro dissection of a serial section does not require active selection of parts of the serial section to be micro dissected.

Throughout the prosecution of this application the examiner has consistently objected to any claim language not taken from the specification. Thus, it is believed that the inclusion of the phrase "without any selection by an investigator" in the claims would lead to a rejection. The phrase "unattendedly micro dissecting" is based on explicit language of the specification and its meaning is clear from that language.

Further, in claim construction the applicant can be his own lexicographer. For example, in *Phillips v. AWH Industries,* 415 F.3d 1303, 1216 (Fed. Cir. 2005) it is stated that: "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases the inventor's lexicography governs."

In the present application, the specification, in the section entitled "Tissue Rasterization" (7:31 to 8:10), cites the Cheung article as allowing for "unattended section incising of a large number of specimens." Although Cheung is not incorporated by reference, since it is not required for an enabling disclosure, the contents of Cheung clearly illustrated the patentee's

definition as presented in the specification and how the terms would be understood by a person of skill in the art reading the claim in light of the specification.

As stated in Cheung (Attached) under Robotic Features: "The AECOM arrayer...generates high density, gridded arrays of cDNA ...material on glass surfaces. The robot is designed to automatically collect samples. (page 15). The motorized stage executes a programmed comb scan pattern that sequentially traverses the microscope slide in the X direction and then steps a pixel width in the Y direction, producing a bi-directional raster pattern. (page 17)"

Accordingly, specific citations to the specification have been provided that make clear that the "unattended micro dissection" phrase would be clearly understood by the person of ordinary skill in the art to not require active selection of parts of the serial section to be micro dissected.

DEPENDENT CLAIMS 2, 9-10.

The dependent claims are allowable for the same reasons as the base claim.

II. Obviousness

INDEPENDENT CLAIMS 1, 4 7, AND 11

The Cited References

1. Heppelmann

Heppelmann discloses two different techniques for three-dimensional reconstruction of extended fine tissue structures: a re-embedding technique and a serial section-ESI technique. It also describes true-to-scale three-dimensional reconstructions.

In the re-embedding technique, the extended fine tissue structure is cut into semi-thin serial sections and the semi-thin sections are examined under oil immersion and photographed. If a semi-thin section is selected for ultra-structural examination then the semi-thin section is re-embedded and converted into a series of ultra-thin sections for viewing the ultra-structural detail of the tissue within that section. Heppelmann, page 164, Re-embedding technique, first and second paragraphs.

Further, in the serial section-ESI technique, a set of serial sections is cut and analyzed utilizing ESI. Heppelmann mentions cutting a complete set of alternate semi- and ultra-thin sections of a tissue block. However, all of these sections are then mounted, in their entirety, in sequence on a mesh transmission grid and imaged using ESI. Id., page 165, first paragraph.

The result of the Heppelmann product is a series of images of the sections, as depicted on the left side of Fig. 4 of Heppelmann, which can be used to form a 3-D reconstruction, as depicted on the right side of Fig. 4. The serial sections on the left side of Fig. 4 form the x,y planes of the 3-D structure and the location of the sections in the 3-D structure is indicated by a z coordinate.

2. Cole

The reference Cole teaches the use of histologically cut serial sections to precisely identify specific tumor cells within the prostate gland which are then selected and excised for microarray analysis of expression activity.

In Cole, a 3-D representation of a prostate gland is formed by stacking whole-mount transverse sections cut from the sample. Each serial section may be viewed and is annotated to show the locations where cell populations have been dissected and analyzed. By interactively clicking on these annotations the user can query a database for data related to a selected cell population. In Cole the selection of the cells to be analyzed occurs prior to the dissection of those cells, and those cells are a specific subset of the cells that make up the entirety of the prostate tissue contained in the series of transverse sections.

3. Farr

The Farr reference merely shows that one can study specific cells for a set of several biological parameters at once and includes graphs depicting the relative concentration of a specific chemical as a function of various concentrations of another chemical.

4. Emmert-Buck

Emmert-Buck discloses placing a thin transparent film over a tissue section, visualizing the tissue section microscopically, and selectively adhering the cells of interest within the tissue section to the film with a fixed-position, short-duration, focused pulse from an infrared laser. The adhered section is removed from the serial section providing the image data.

5. Lemelson

Lemelson describes the well-known techniques of generating morphological image data described in the background section of the patent application. Scanning signals are generated by well-known scanning devices such as MRI, CAT, or PET, and the scanning signals are computer processed to generate cross-sectional views. The views are analyzed to define the borders of anatomical structures which may be further processed to provide code signals indicative of coordinate locations of these structures. (9:25-43).

The Examiner's Reasoning

The examiner finds applicants' arguments that none of the references disclose the step of unattendedly micro dissecting each serial sample, assigning code, analyzing the sample, and superimposing or linking the biological data unpersuasive. It is stated that Heppelmann et al. recite micro-dissecting serial samples and Emmert-Buck et al. recite the steps including unattendedly micro-dissecting serial samples. (Office Action; page 16); that Lemelson and Bogen et al. recite steps of assigning code; Cole et al. recite steps of analyzing a sample, and Cole et al. and Farr et al. recite steps of superimposing or linking data. It is stated that Emmert-Buck et al., at page 998, third column, first full paragraph and the abstract, describe automatic micro-dissection without manual procedures.

A. **All the Limitations of Independent Claim 1, 4, 7 and 11 are not fairly Taught or Suggested by the Cited References.**

MPEP §2143.03 requires that all claim limitations must be taught or suggested by the cited references.

As set forth below, none of the references suggest or teach the steps recited in claim 1, 4, 7, and 11.

Independent claims 1, 4, 7, and 11 recite features of unattendedly micro dissecting each serial sample into a set of micro dissected section samples, assigning a code to each micro dissected section sample indicating the location of the coded micro dissected section sample in the multi-dimensional image data, analyzing each coded micro dissected section sample to determine biological data characterizing the micro dissected section sample, and superimposing or linking the biological data of the coded micro dissected section sample upon or to volume image data indicated by the code assigned to the coded micro dissected section sample.

These steps are not taught or suggested in the references.

The examiner states regarding Heppelmann that:

> Heppelmann et al. describes cutting the second set of sections (for ultrastructural examination) and mounting them on single-slot grids to be further examined (page 164, last paragraph) which represents creating a grid pattern across each serial section to create a set of incised section samples for each serial section of the second set, as stated in claims 1, 7, and 11. Heppelmann et al. describe the sections were mounted in

> sequence on mesh grids (page 165, lines 12-14) which is reasonably interpreted to be associating each incised section sample with a unique set of indices as it has grids (x and y coordinates) with each individual sample placed in a known location as stated in claims 1 and 4.

However, in Heppelmann there is no teaching or suggestion of unattendedly micro dissecting a serial section into a set of micro dissected section samples or of assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix. In Heppelmann, incising the serial sections would be contrary to the teaching of the reference since the serial sections are analyzed by a microscope. Incising or micro dissecting the sections would destroy their utility for that purpose.

Further, there is no suggestion of assigning a code to coded micro dissected section samples. In Heppelmann there is no analysis of samples for biological activity and hence no data to be mapped to the spatial image. Accordingly, there is no motivation to assign codes to the micro dissected tissue samples.

With regard to Cole the examiner states:

> Cole et al. describe methods for preparing microarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al discuss that the above processes allow for the determination of exact physical relationships between morphological data (one set) on which overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) which represent associating indices from each incised section sample of the second set with indices of the morphological tissue space matrix

However, in the cited sections of Cole et al. there is no discussion or suggestion of micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

In Cole, it is stated that "8 micrometer serial cut slides are prepared from tissue blocks ... revealing all the normal pathology in the Z direction". Thus, the reference teaches that

the specimen can be cut into serial sections. In Fig. 1 various selected sections have been annotated as being of interest. For example, the figure labeled "bird's eye view" depicts the entire structure with multiple transverse views showing areas of anatomical interest. One of these transverse areas is shown in the figure labeled "transverse road map" view with the areas on which experiments have been performed. Note that the transverse section has not been unattendedly micro dissected into a multi-dimensional spatial matrix of coded micro dissected samples as required by claim 1. The micro dissected samples in Cole are not distributed in a matrix but are distributed according to the selection of the investigator that did the section. Nor was the micro dissection unattended, but areas of interest were selected.

Accordingly, there is no teaching or suggestion in Cole of the claimed step of unattendedly micro dissecting the serial section into a set of micro dissected section samples.

With regard to Emmert-Buck the examiner states:

> Emmert-Buck et al. describe a laser applied to specific locations of the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggest incising grid patterns of the tissue and selecting only particular sections.

However, in the cited section of Emmert-Buck there is absolutely no teaching or suggestion of unattendedly micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

The techniques of "visualizing the tissue microscopically, and selectively adhering the cell of interest to the film" described in that reference do not suggest or teach the claimed feature.

Further, the first full paragraph at page 998, col. 3 cited by the examiner as disclosing unattendedly micro dissecting must be considered in the context of the paragraph immediately preceding where it is stated that the cells of interest are selectively adhered to the film. The fact that no manual manipulation is required is inapposite to whether the micro dissection is unattended. The reference must be considered in its entirety, including those sections that would argue against obviousness. Panduit Corp. v. Dennison Manufacturing Company, 227 USPQ 337, 345 (CAFC 1985).

With regard to Lemelson, there is no teaching of unattendedly micro dissecting a serial section sample. Lemelson only relates to digital processing of scanned image data.

Therefore, the claimed feature of unattendedly micro dissecting a serial section into a set of micro dissected section samples and assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix is not taught or suggested in any cited reference.

Further, there is no disclosure of the claimed feature of a code assigned to each micro dissected section sample indicating the location of the coded micro dissected sample in the multidimensional matrix.

B. **The Proposed Modification of Incorporating the features of Cole, Emmert-Buck, Farr, and Lemelson into the three-dimensional reconstruction technique of Heppelmann would change the Principle of Operation of Heppelmann.**

MPEP §2143.01 requires that a prima facie case of obviousness is not established if the proposed modification would change the principle of operation of a reference.

The fundamental principle of operation in the re-embedding technique of Heppelmann, the 3-D model of Cole, and the laser capture micro-dissection of Emmert-Buck is that an area of interest is selected for further analysis from a section being viewed.

In contrast, the method recited in claims 1, 4, 7, and 11 works on a fundamentally different principle of operation in that the serial sections of a biological sample are unattendedly micro dissected into serial sections without any selection, and the micro dissected sections are further analyzed. This allows selection of any part of a serial section for further investigation to occur at any time subsequent to the micro dissecting because the complete data set is available to be mapped onto the multidimensional image matrix. Thus, the present system lends itself to a survey approach rather than a directed selection approach. As described in [35] of the present application this allows for unattended section incising of a large number of specimens.

In contrast, for example, in Cole if an investigator needed data at a location that had not been previously selected, dissected, and analyzed it would be necessary to go back and dissect another cell population for analysis, which might not be possible. That is because in Cole the investigator selects areas of interest for analysis. As described at paragraph [18], describing Cole, of the present application:

> It should be noted that this study focused on only small groups of specific tissue areas, since the microdissection approach requires a skilled operator and is extremely exacting work. Tissue that isn't used for expression analysis is stained for anatomical reconstruction of the gland architecture, rendering it unusable for further expression analysis. Since this approach is targeted to specific areas of the tissue, it is most useful for specifically targeted studies, and is poorly suited for survey-based exploratory analysis.

In Emmert-Buck the investigator selectively adheres cells of interest to the film.

Further, with regard to Heppelmann, the proposed combination would change the principle of operation of the primary reference and render it inoperable. If the serial section of Heppelmann were micro dissected it could not be used for the next step of ultra-structural analysis since the structure of the serial section would have been destroyed.

C. **There is No Teaching in the References Suggesting the Combination of the References.**

MPEP §2143.01 requires that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching or suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

It has been clearly established above that the claimed features are not taught or suggested by the cited references. However, even if the various features were disclosed, there is no teaching, suggestion, or motivation in the references to combine the features as recited in the pending claims.

The various references have been described in detail above. The Office Action at pages 12-14 lists a series of motivations to combine the various features as recited in the claims. However, none of the listed motivations meet the recited claim limitations. As described above, Heppelmann, Emmert-Buck, and Cole teach away from the steps of unattendedly micro dissecting the section samples. The references Farr, Lemelson, and Bogen are unrelated to the claimed invention.

For example, at page 13 of the Office Action, it is stated that a PHOSA would have been motivated to create tissue sections of Heppelmann, Cole, and Farr with the automated laser

capture micro dissection as stated by Emmert-Buck in order to provide ease, precision, and efficiency in a rapid one-step procurement of selected targeted human cells from a section of complex, heterogeneous tissue.

However, this cited motivation actually teaches away from the claimed combination as described above. Unattended micro dissection is not utilized for procurement of selected cells but for a survey approach to the whole tissue section.

Accordingly, none of the references discloses the steps recited in independent claims 1, 7 and 11 and a *prima facie* case of obviousness has not been established.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 944-3320.

Respectfully submitted,

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